Caution in the Use of Nonlinear Effects as a Mechanistic Tool for Catalytic Enantioconvergent Reactions: Intrinsic Negative Nonlinear Effects in the Absence of Higher-Order Species

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Supporting Information

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I. Mathematical Analysis

The appearance of a nonlinear effect in the system illustrated in eqs 1–4, explained in the Article in a descriptive way, can also be demonstrated using a rigorous mathematical analysis.

$$SM_R \xrightarrow[k_1]{CAT_R} P_R \qquad (1)$$

$$SM_S \xrightarrow[k_2]{CAT_R} P_R \qquad (2)$$

$$SM_R \xrightarrow[k_2]{CAT_S} P_S \qquad (3)$$

$$SM_S \xrightarrow[k_1]{CAT_S} P_S \qquad (4)$$

SM_R and SM_S are enantiomers.
CAT_R and CAT_S are enantiomers.
P_R and P_S are enantiomers.

Kagan has established that the racemic starting material in such network of reactions will undergo a kinetic resolution according to eq 5,[1] which includes the ee of the catalyst (ee_{CAT}). Upon comparison with the equation for a normal kinetic resolution,[2] the left-hand side of eq 5 can be viewed as the selectivity factor corrected for the enantiomeric impurity of the catalyst; its value varies between 1 and s for $ee_{CAT} = 0$ (racemic) and 1 (enantiopure), respectively.

$$\frac{s + 1 + ee_{CAT}(s - 1)}{s + 1 + ee_{CAT}(1 - s)} = \frac{\ln[(1 - c)(1 - ee_{SM})]}{\ln[(1 - c)(1 + ee_{SM})]} \quad (5)$$

ee_{CAT} = ee of the catalyst ($0 \le ee_{CAT} \le 1$)

Thus, for $s > 1$, with increasing conversion, the unreacted starting will progressively undergo an enrichment in the enantiomer that is mismatched with the major enantiomer of the catalyst present in the reaction mixture.

With regard to the product, the instantaneous enantioselectivity ($(d[P_R]/dt)/(d[P_S]/dt)$) for the network of interest is described by eq 6 (see below for its derivation). This selectivity depends both on the ee of the catalyst (ee_{CAT}) and on the instantaneous ee of the unreacted starting material (ee_{SM}).

$$\frac{\frac{d[P_R]}{dt}}{\frac{d[P_S]}{dt}} = \frac{s + 1 + ee_{SM}(1 - s)}{s + 1 + ee_{SM}(s - 1)} \cdot \frac{1 + ee_{CAT}}{1 - ee_{CAT}} \quad (6)$$

$$= \frac{s + 1 + ee_{SM}(1 - s)}{s + 1 + ee_{SM}(s - 1)} \cdot er_{CAT}$$

$$= X \cdot er_{CAT}$$

P_R = major enantiomer of product
er_{CAT} = enantiomeric ratio of the catalyst (≥ 1)
ee_{SM} = ee of SM_S at a given time ($0 \le ee_{SM} \le 1$)

Eq 6 shows that for $ee_{SM} = 0$, the instantaneous enantioselectivity equals er_{CAT}, i.e., at the outset of the reaction (starting material is racemic), the ee of the product is the same as the ee of the catalyst (as clearly visible in Figure 4 in the Article). Further analysis of eq 6 reveals that, as the reaction progresses and the mixture becomes enriched in the less-reactive enantiomer of the starting material ($ee_{SM} > 0$), the instantaneous enantioselectivity falls below er_{CAT} ($X < 1$). In other words, as the mixture becomes enriched in the enantiomer of the starting material that matches the minor enantiomer of the catalyst, the instantaneous enantioselectivity diminishes, leading to the negative nonlinear effect.

Derivation of eq 6:

The rates of formation of the enantiomeric products can be expressed as ($s = k_1/k_2$):

[1] Luukas, T. O.; Girard, C.; Fenwick, D. R.; Kagan, H. B. *J. Am. Chem. Soc.* **1999**, *121*, 9299–9306.

[2] Kagan, H. B.; Fiaud, J. C. In *Topics in Stereochemistry*; Eliel, E. L., Wilen, S. H., Eds.; John Wiley & Sons: Hoboken, NJ, 1988; Vol. 18, pp 249–330.

$$\frac{d[P_R]}{dt} = k_1[CAT_R][SM_R] + k_2[CAT_R][SM_S] = k_2(s[SM_R] + [SM_S])\cdot[CAT_R]$$

$$\frac{d[P_S]}{dt} = k_2[CAT_S][SM_R] + k_1[CAT_S][SM_S] = k_2(s[SM_S] + [SM_R])\cdot[CAT_S]$$

Thus, taking into account the relationship between er and ee ($er = \frac{1+ee}{1-ee}$), the instantaneous enantioselectivity can be expressed as:

$$\frac{\frac{d[P_R]}{dt}}{\frac{d[P_S]}{dt}} = \frac{k_2(s[SM_R] + [SM_S])\cdot[CAT_R]}{k_2(s[SM_S] + [SM_R])\cdot[CAT_S]} = \frac{s[SM_R] + [SM_S]}{s[SM_S] + [SM_R]} \cdot \frac{[CAT_R]}{[CAT_S]}$$

$$= \frac{s\cdot\frac{[SM_R]}{[SM_R]} + \frac{[SM_S]}{[SM_R]}}{s\cdot\frac{[SM_S]}{[SM_R]} + \frac{[SM_R]}{[SM_R]}} \cdot er_{CAT} = \frac{s + er_{SM}}{s\cdot er_{SM} + 1} \cdot er_{CAT} = \frac{s + \frac{1+ee_{SM}}{1-ee_{SM}}}{s\cdot\frac{1+ee_{SM}}{1-ee_{SM}} + 1} \cdot \frac{1+ee_{CAT}}{1-ee_{CAT}}$$

$$= \frac{s(1-ee_{SM}) + 1 + ee_{SM}}{s(1+ee_{SM}) + 1 - ee_{SM}} \cdot \frac{1+ee_{CAT}}{1-ee_{CAT}} = \frac{s + 1 + ee_{SM}(1-s)}{s + 1 + ee_{SM}(s-1)} \cdot \frac{1+ee_{CAT}}{1-ee_{CAT}}$$

II. Details of kinetics simulations

Table S1 contains the initial concentrations (M) and the values of the rate constants ($M^{-1}\cdot s^{-1}$) used in the kinetics simulations of the model depicted in eqs 1–4 in the Article. Lines connecting the simulated data points in Figures 4 and 5 were generated using the interpolation algorithm implemented in Microsoft Excel 2013 ("smoothed lines").

Table S1

Entry		$[SM_R]_0$	$[SM_S]_0$	$[CAT_R]_0$	$[CAT_S]_0$	k_1	k_2
	Figure 4a						
1	s = 10; ee_{CAT} = 0%	0.5	0.5	0.005	0.005	10	1
2	s = 10; ee_{CAT} = 25%	0.5	0.5	0.00625	0.00375	10	1
3	s = 10; ee_{CAT} = 50%	0.5	0.5	0.0075	0.0025	10	1
4	s = 10; ee_{CAT} = 75%	0.5	0.5	0.00875	0.00125	10	1
5	s = 10; ee_{CAT} = 100%	0.5	0.5	0.01	0	10	1
	Figure 4b						
6	s = 1; ee_{CAT} = 50%	0.5	0.5	0.0075	0.0025	1	1
7	s = 3; ee_{CAT} = 50%	0.5	0.5	0.0075	0.0025	3	1
8	s = 10; ee_{CAT} = 50%	0.5	0.5	0.0075	0.0025	10	1
9	s = 50; ee_{CAT} = 50%	0.5	0.5	0.0075	0.0025	50	1
10	s = 100; ee_{CAT} = 50%	0.5	0.5	0.0075	0.0025	100	1
	Figures 5a and 5b						
11	s = 3; ee_{CAT} = 0%	0.5	0.5	0.005	0.005	3	1
12	s = 3; ee_{CAT} = 10%	0.5	0.5	0.0055	0.0045	3	1
13	s = 3; ee_{CAT} = 20%	0.5	0.5	0.0060	0.0040	3	1
14	s = 3; ee_{CAT} = 30%	0.5	0.5	0.0065	0.0035	3	1
15	s = 3; ee_{CAT} = 40%	0.5	0.5	0.0070	0.0030	3	1
16	s = 3; ee_{CAT} = 50%	0.5	0.5	0.0075	0.0025	3	1
17	s = 3; ee_{CAT} = 60%	0.5	0.5	0.0080	0.0020	3	1
18	s = 3; ee_{CAT} = 70%	0.5	0.5	0.0085	0.0015	3	1
19	s = 3; ee_{CAT} = 80%	0.5	0.5	0.0090	0.0010	3	1
20	s = 3; ee_{CAT} = 90%	0.5	0.5	0.0095	0.0005	3	1
21	s = 3; ee_{CAT} = 100%	0.5	0.5	0.01	0	3	1
22	s = 10; ee_{CAT} = 0%	0.5	0.5	0.005	0.005	10	1
23	s = 10; ee_{CAT} = 10%	0.5	0.5	0.0055	0.0045	10	1
24	s = 10; ee_{CAT} = 20%	0.5	0.5	0.0060	0.0040	10	1
25	s = 10; ee_{CAT} = 30%	0.5	0.5	0.0065	0.0035	10	1
26	s = 10; ee_{CAT} = 40%	0.5	0.5	0.0070	0.0030	10	1
27	s = 10; ee_{CAT} = 50%	0.5	0.5	0.0075	0.0025	10	1
28	s = 10; ee_{CAT} = 60%	0.5	0.5	0.0080	0.0020	10	1
29	s = 10; ee_{CAT} = 70%	0.5	0.5	0.0085	0.0015	10	1
30	s = 10; ee_{CAT} = 80%	0.5	0.5	0.0090	0.0010	10	1
31	s = 10; ee_{CAT} = 90%	0.5	0.5	0.0095	0.0005	10	1
32	s = 10; ee_{CAT} = 100%	0.5	0.5	0.01	0	10	1
33	s = 50; ee_{CAT} = 0%	0.5	0.5	0.005	0.005	50	1
34	s = 50; ee_{CAT} = 10%	0.5	0.5	0.0055	0.0045	50	1
35	s = 50; ee_{CAT} = 20%	0.5	0.5	0.0060	0.0040	50	1
36	s = 50; ee_{CAT} = 30%	0.5	0.5	0.0065	0.0035	50	1
37	s = 50; ee_{CAT} = 40%	0.5	0.5	0.0070	0.0030	50	1

38	s = 50; ee_{CAT} = 50%	0.5	0.5	0.0075	0.0025	50	1
39	s = 50; ee_{CAT} = 60%	0.5	0.5	0.0080	0.0020	50	1
40	s = 50; ee_{CAT} = 70%	0.5	0.5	0.0085	0.0015	50	1
41	s = 50; ee_{CAT} = 80%	0.5	0.5	0.0090	0.0010	50	1
42	s = 50; ee_{CAT} = 90%	0.5	0.5	0.0095	0.0005	50	1
43	s = 50; ee_{CAT} = 95%	0.5	0.5	0.00975	0.00025	50	1
44	s = 50; ee_{CAT} = 97.5%	0.5	0.5	0.009875	0.000125	50	1
45	s = 50; ee_{CAT} = 100%	0.5	0.5	0.01	0	50	1
46	s = 100; ee_{CAT} = 0%	0.5	0.5	0.005	0.005	100	1
47	s = 100; ee_{CAT} = 10%	0.5	0.5	0.0055	0.0045	100	1
48	s = 100; ee_{CAT} = 20%	0.5	0.5	0.0060	0.0040	100	1
49	s = 100; ee_{CAT} = 30%	0.5	0.5	0.0065	0.0035	100	1
50	s = 100; ee_{CAT} = 40%	0.5	0.5	0.0070	0.0030	100	1
51	s = 100; ee_{CAT} = 50%	0.5	0.5	0.0075	0.0025	100	1
52	s = 100; ee_{CAT} = 60%	0.5	0.5	0.0080	0.0020	100	1
53	s = 100; ee_{CAT} = 70%	0.5	0.5	0.0085	0.0015	100	1
54	s = 100; ee_{CAT} = 80%	0.5	0.5	0.0090	0.0010	100	1
55	s = 100; ee_{CAT} = 90%	0.5	0.5	0.0095	0.0005	100	1
56	s = 100; ee_{CAT} = 95%	0.5	0.5	0.00975	0.00025	100	1
57	s = 100; ee_{CAT} = 97.5%	0.5	0.5	0.009875	0.000125	100	1
58	s = 100; ee_{CAT} = 100%	0.5	0.5	0.01	0	100	1

III. Simulations of a two-step enantioconvergent reaction

In section I, we have demonstrated that the nonlinear effect can already arise in the simplest possible set of four reactions representing an enatioconvergent catalytic process (eqs 1–4). Herein, we evaluate by kinetics simulations the behavior an enantioconvergent catalytic reaction, following a more realistic two-step model mechanism shown below, involving the formation of a common intermediate from the two enantiomers of the starting material. All steps are considered strictly irreversible in the simulations.

Figure S1 depicts the simulated ee_P vs. ee_{CAT} plots in the scenario, wherein the first step is rate-determining (k_1 and k_2 << k_R and k_S) and the second step is not fully selective (k_R/k_S=9; the results are at 90% conversion).

The nonlinear effect is present, but compared to the fully selective reaction, all the lines intersect at ee_P = 80% for ee_{CAT} = 100%, which is the maximal attainable product ee under these conditions (ee_{MAX}). Hence, a reaction with a catalyst that is not fully selective will also display the inherent nonlinear effect.

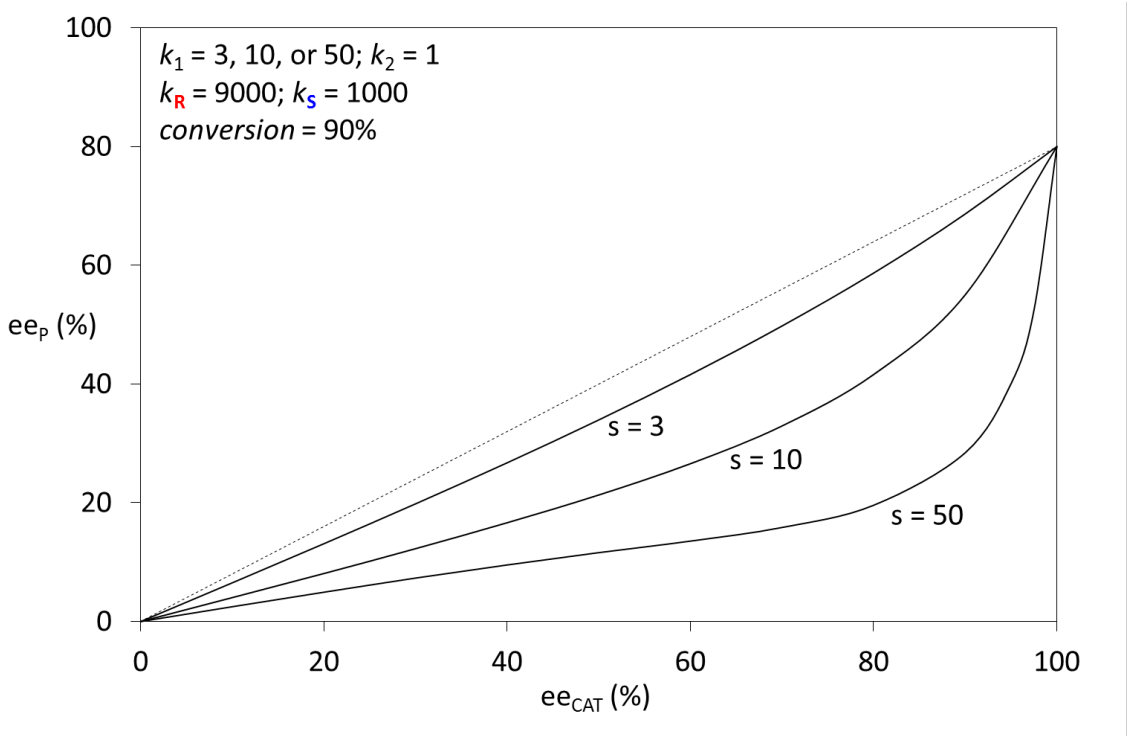

Figure S1.

Figure S2 depicts the simulated ee_P vs. ee_{CAT} plots for the reactions with varying degree of rate-control by the respective steps of the mechanism. In all cases, the first step displays a selectivity factor of 50 (k_1/k_2 = 50). For simplicity, the second step was set to be fully selective (k_S = 0; the results are at 90% conversion).

The nonlinear effect is present only when the first step is at least partially rate-determining, and its magnitude rises with increasing degree of rate-control by this step. In particular, for k_R = 1000 (the first step is fully rate-determining), the simulated curve is identical to the one depicted in Figure 5b in the Article (for s = 50). This is because, although in all cases the starting material undergoes exactly the same kinetic resolution, the rise in ee_{SM} can only affect the overall kinetics, and in turn the selectivity of the product formation, if SM is involved in the rate determining step.

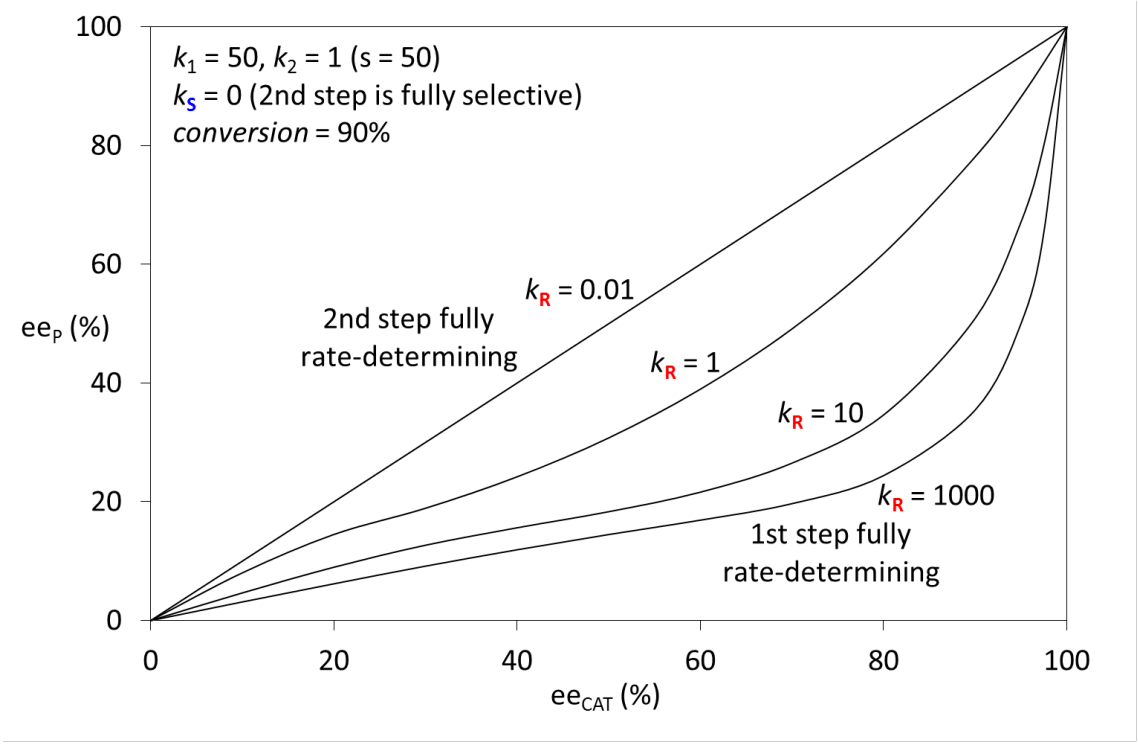

Figure S2.

Table S2 contains the initial concentrations (M) and the values of the rate constants ($M^{-1}\cdot s^{-1}$ and s^{-1} for k_1, k_2 and k_R, k_S, respectively) used in the kinetics simulations of the model depicted above. Lines connecting the simulated data points in Figures S1–S2 were generated using the interpolation algorithm implemented in Microsoft Excel 2013 ("smoothed lines").

Table S2

Entry		$[SM_R]_0$	$[SM_S]_0$	$[CAT_R]_0$	$[CAT_S]_0$	k_1	k_2	k_R	k_S
Figure S1									
1	s = 3; ee_{CAT} = 0%	0.5	0.5	0.005	0.005	3	1	9000	1000
2	s = 3; ee_{CAT} = 10%	0.5	0.5	0.0055	0.0045	3	1	9000	1000
3	s = 3; ee_{CAT} = 20%	0.5	0.5	0.0060	0.0040	3	1	9000	1000

4	s = 3; ee_{CAT} = 30%	0.5	0.5	0.0065	0.0035	3	1	9000	1000
5	s = 3; ee_{CAT} = 40%	0.5	0.5	0.0070	0.0030	3	1	9000	1000
6	s = 3; ee_{CAT} = 50%	0.5	0.5	0.0075	0.0025	3	1	9000	1000
7	s = 3; ee_{CAT} = 60%	0.5	0.5	0.0080	0.0020	3	1	9000	1000
8	s = 3; ee_{CAT} = 70%	0.5	0.5	0.0085	0.0015	3	1	9000	1000
9	s = 3; ee_{CAT} = 80%	0.5	0.5	0.0090	0.0010	3	1	9000	1000
10	s = 3; ee_{CAT} = 90%	0.5	0.5	0.0095	0.0005	3	1	9000	1000
11	s = 3; ee_{CAT} = 100%	0.5	0.5	0.01	0	3	1	9000	1000
12	s = 10; ee_{CAT} = 0%	0.5	0.5	0.005	0.005	10	1	9000	1000
13	s = 10; ee_{CAT} = 10%	0.5	0.5	0.0055	0.0045	10	1	9000	1000
14	s = 10; ee_{CAT} = 20%	0.5	0.5	0.0060	0.0040	10	1	9000	1000
15	s = 10; ee_{CAT} = 30%	0.5	0.5	0.0065	0.0035	10	1	9000	1000
16	s = 10; ee_{CAT} = 40%	0.5	0.5	0.0070	0.0030	10	1	9000	1000
17	s = 10; ee_{CAT} = 50%	0.5	0.5	0.0075	0.0025	10	1	9000	1000
18	s = 10; ee_{CAT} = 60%	0.5	0.5	0.0080	0.0020	10	1	9000	1000
19	s = 10; ee_{CAT} = 70%	0.5	0.5	0.0085	0.0015	10	1	9000	1000
20	s = 10; ee_{CAT} = 80%	0.5	0.5	0.0090	0.0010	10	1	9000	1000
21	s = 10; ee_{CAT} = 90%	0.5	0.5	0.0095	0.0005	10	1	9000	1000
22	s = 10; ee_{CAT} = 100%	0.5	0.5	0.01	0	10	1	9000	1000
23	s = 50; ee_{CAT} = 0%	0.5	0.5	0.005	0.005	50	1	9000	1000
24	s = 50; ee_{CAT} = 10%	0.5	0.5	0.0055	0.0045	50	1	9000	1000
25	s = 50; ee_{CAT} = 20%	0.5	0.5	0.0060	0.0040	50	1	9000	1000
26	s = 50; ee_{CAT} = 30%	0.5	0.5	0.0065	0.0035	50	1	9000	1000
27	s = 50; ee_{CAT} = 40%	0.5	0.5	0.0070	0.0030	50	1	9000	1000
28	s = 50; ee_{CAT} = 50%	0.5	0.5	0.0075	0.0025	50	1	9000	1000
29	s = 50; ee_{CAT} = 60%	0.5	0.5	0.0080	0.0020	50	1	9000	1000
30	s = 50; ee_{CAT} = 70%	0.5	0.5	0.0085	0.0015	50	1	9000	1000
31	s = 50; ee_{CAT} = 80%	0.5	0.5	0.0090	0.0010	50	1	9000	1000
32	s = 50; ee_{CAT} = 90%	0.5	0.5	0.0095	0.0005	50	1	9000	1000
33	s = 50; ee_{CAT} = 95%	0.5	0.5	0.00975	0.00025	50	1	9000	1000
34	s = 50; ee_{CAT} = 97.5%	0.5	0.5	0.009875	0.000125	50	1	9000	1000
35	s = 50; ee_{CAT} = 100%	0.5	0.5	0.01	0	50	1	9000	1000
Figure S2									
36	k_R = 0.01; ee_{CAT} = 0%	0.5	0.5	0.005	0.005	50	1	0.01	0
37	k_R = 0.01; ee_{CAT} = 10%	0.5	0.5	0.0055	0.0045	50	1	0.01	0
38	k_R = 0.01; ee_{CAT} = 20%	0.5	0.5	0.0060	0.0040	50	1	0.01	0
39	k_R = 0.01; ee_{CAT} = 30%	0.5	0.5	0.0065	0.0035	50	1	0.01	0
40	k_R = 0.01; ee_{CAT} = 40%	0.5	0.5	0.0070	0.0030	50	1	0.01	0
41	k_R = 0.01; ee_{CAT} = 50%	0.5	0.5	0.0075	0.0025	50	1	0.01	0
42	k_R = 0.01; ee_{CAT} = 60%	0.5	0.5	0.0080	0.0020	50	1	0.01	0
43	k_R = 0.01; ee_{CAT} = 70%	0.5	0.5	0.0085	0.0015	50	1	0.01	0
44	k_R = 0.01; ee_{CAT} = 80%	0.5	0.5	0.0090	0.0010	50	1	0.01	0
45	k_R = 0.01; ee_{CAT} = 90%	0.5	0.5	0.0095	0.0005	50	1	0.01	0
46	k_R = 0.01; ee_{CAT} = 100%	0.5	0.5	0.01	0	50	1	0.01	0
47	k_R = 1; ee_{CAT} = 0%	0.5	0.5	0.005	0.005	50	1	1	0
48	k_R = 1; ee_{CAT} = 10%	0.5	0.5	0.0055	0.0045	50	1	1	0
49	k_R = 1; ee_{CAT} = 20%	0.5	0.5	0.0060	0.0040	50	1	1	0
50	k_R = 1; ee_{CAT} = 30%	0.5	0.5	0.0065	0.0035	50	1	1	0
51	k_R = 1; ee_{CAT} = 40%	0.5	0.5	0.0070	0.0030	50	1	1	0

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53	k_R = 1; ee_{CAT} = 60%	0.5	0.5	0.0080	0.0020	50	1	1	0
54	k_R = 1; ee_{CAT} = 70%	0.5	0.5	0.0085	0.0015	50	1	1	0
55	k_R = 1; ee_{CAT} = 80%	0.5	0.5	0.0090	0.0010	50	1	1	0
56	k_R = 1; ee_{CAT} = 90%	0.5	0.5	0.0095	0.0005	50	1	1	0
57	k_R = 1; ee_{CAT} = 95%	0.5	0.5	0.00975	0.00025	50	1	1	0
58	k_R = 1; ee_{CAT} = 100%	0.5	0.5	0.01	0	50	1	1	0
59	k_R = 10; ee_{CAT} = 0%	0.5	0.5	0.005	0.005	50	1	10	0
60	k_R = 10; ee_{CAT} = 10%	0.5	0.5	0.0055	0.0045	50	1	10	0
61	k_R = 10; ee_{CAT} = 20%	0.5	0.5	0.0060	0.0040	50	1	10	0
62	k_R = 10; ee_{CAT} = 30%	0.5	0.5	0.0065	0.0035	50	1	10	0
63	k_R = 10; ee_{CAT} = 40%	0.5	0.5	0.0070	0.0030	50	1	10	0
64	k_R = 10; ee_{CAT} = 50%	0.5	0.5	0.0075	0.0025	50	1	10	0
65	k_R = 10; ee_{CAT} = 60%	0.5	0.5	0.0080	0.0020	50	1	10	0
66	k_R = 10; ee_{CAT} = 70%	0.5	0.5	0.0085	0.0015	50	1	10	0
67	k_R = 10; ee_{CAT} = 80%	0.5	0.5	0.0090	0.0010	50	1	10	0
68	k_R = 10; ee_{CAT} = 90%	0.5	0.5	0.0095	0.0005	50	1	10	0
69	k_R = 10; ee_{CAT} = 95%	0.5	0.5	0.00975	0.00025	50	1	10	0
70	k_R = 10; ee_{CAT} = 97.5%	0.5	0.5	0.009875	0.000125	50	1	10	0
71	k_R = 10; ee_{CAT} = 100%	0.5	0.5	0.01	0	50	1	10	0
72	k_R = 1000; ee_{CAT} = 0%	0.5	0.5	0.005	0.005	50	1	1000	0
73	k_R = 1000; ee_{CAT} = 10%	0.5	0.5	0.0055	0.0045	50	1	1000	0
74	k_R = 1000; ee_{CAT} = 20%	0.5	0.5	0.0060	0.0040	50	1	1000	0
75	k_R = 1000; ee_{CAT} = 30%	0.5	0.5	0.0065	0.0035	50	1	1000	0
76	k_R = 1000; ee_{CAT} = 40%	0.5	0.5	0.0070	0.0030	50	1	1000	0
77	k_R = 1000; ee_{CAT} = 50%	0.5	0.5	0.0075	0.0025	50	1	1000	0
78	k_R = 1000; ee_{CAT} = 60%	0.5	0.5	0.0080	0.0020	50	1	1000	0
79	k_R = 1000; ee_{CAT} = 70%	0.5	0.5	0.0085	0.0015	50	1	1000	0
80	k_R=1000; ee_{CAT} = 80%	0.5	0.5	0.0090	0.0010	50	1	1000	0
81	k_R=1000; ee_{CAT} = 90%	0.5	0.5	0.0095	0.0005	50	1	1000	0
82	k_R=1000; ee_{CAT} = 95%	0.5	0.5	0.00975	0.00025	50	1	1000	0
83	k_R=1000;ee_{CAT} = 97.5%	0.5	0.5	0.009875	0.000125	50	1	1000	0
84	k_R=1000; ee_{CAT} = 100%	0.5	0.5	0.01	0	50	1	1000	0

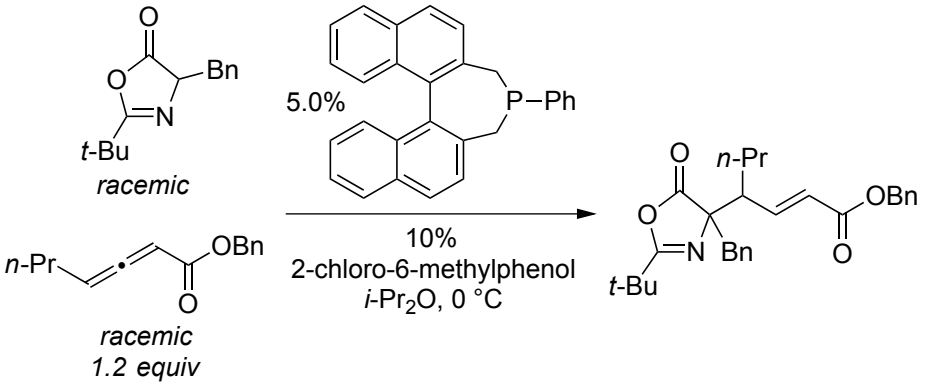
IV. Experimental procedures

General

Phosphepine **1**,[3] (±)-4-benzyl-2-(*tert*-butyl)oxazol-5(4*H*)-one,[4] benzyl (±)-hepta-2,3-dienoate,[4] and (±)-cyclohex-2-en-1-yl methyl carbonate[5] were synthesized according to published procedures. Anhydrous dichloromethane was purified prior to use by passage through a column of neutral alumina under argon. Degassed H_2O was obtained by subjecting deionized water to 5 freeze-pump-thaw cycles. All other materials were purchased from commercial suppliers and used as received.

HPLC analyses were carried out on Agilent 1100 or Waters e2695 series systems with Daicel CHIRALPAK columns (4.6 × 250 mm, particle size 5 μm). GC analyses were carried out on a Varian 3900 system.

Product ee vs. catalyst ee in the phosphine-catalyzed γ-addition reaction (Figure 7)



In a nitrogen-filled glovebox, the appropriate amounts (see Table S3, below) of stock solutions of (*S*)–**1** (0.0125 M in anhydrous diisopropyl ether) and (*R*)–**1** (0.0125 M in anhydrous diisopropyl ether) were mixed in an oven-dried vial (total solution volume: 200 μL; 0.0025 mmol). Then, stock solutions of (±)-4-benzyl-2-(*tert*-butyl)oxazol-5(4*H*)-one (0.50 M in anhydrous diisopropyl ether; 100 μL, 0.050 mmol) and 2-chloro-6-methylphenol (0.10 M in anhydrous diisopropyl ether; 50 μL, 0.0050 mmol) were added, and the vial was cooled to 0 °C. A stock solution of benzyl (±)-hepta-2,3-dienoate (0.40 M in anhydrous diisopropyl ether; 150 μL, 0.060 mmol), pre-cooled to 0 °C, was added, and the reaction mixture was stirred at 0 °C for 24 h. Then, a solution of *tert*-butyl hydroperoxide (5.0-6.0 M in decane; 5 μL) was added to quench the reaction. The mixture was stirred at 0 °C for an additional 10 min, and then the vial was removed from the glovebox and warmed to rt. Dibenzyl ether (internal standard; 9.5 μL, 9.9 mg, 0.050 mmol) was added, and then the reaction mixture was concentrated under reduced pressure. The percent conversion was determined through ^{1}H NMR analysis to be >90% for all of the reactions. The product and the oxidized catalyst were purified by preparative TLC (silica; hexanes:ethyl acetate/9:1 and ethyl acetate, respectively), and their ee was determined by chiral HPLC analysis: product (major diastereomer): CHIRALPAK IC column, hexanes:2-propanol/98:2, 1.0 mL/min

[3] Junge, K.; Hagemann, B.; Enthaler,S.; Spannenberg, A.; Michalik, M.; Oehme, G.; Monsees, A.; Riermeier, T.; Beller, M. *Tetrahedron: Asymmetry* **2004**, *15*, 2621–2631.
[4] Kalek, M.; Fu, G. C. *J. Am. Chem. Soc.* **2015**, *137*, 9438–9442.
[5] Ramadhar, T.R.; Kawakami, J.-i.; Lough, A. J.; Batey, R. A. *Org. Lett.* **2010**, *12*, 4446–4449.

flow-rate, retention times: 6.2 min (*S*,*R*), 8.4 min (*R*,*S*); oxide of ligand **1**: CHIRALPAK IA column, hexanes:2-propanol/6:4, 1.0 mL/min flow-rate, retention times: 7.9 min (*S*), 14.0 min (*R*).

Table S3

Entry	Volume of (*S*)–**1** solution (μL)	Volume of (*R*)–**1** solution (μL)
1	0	200
2	20	180
3	40	160
4	60	140
5	80	120
6	100	100
7	120	80
8	140	60
9	160	40
10	180	20
11	200	0

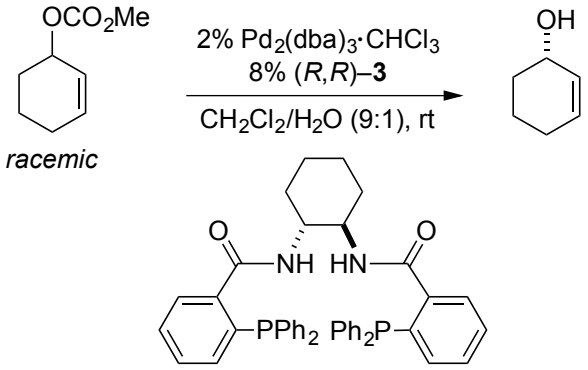
The second series of reactions was carried out in a similar manner, except that the reactions were quenched after 10 min, instead of 24 h. Analysis via ^{1}H NMR spectroscopy showed that all of the reactions in this series had proceeded to ~10% conversion.

Table S4

Entry	ee_{CAT} (%)	ee_P (%)	conversion (allene; %)
"~10% conversion"			
1	–100 (*R*)	–90 (*R*,*S*)	9
2	–78	–72	9
3	–58	–52	9
4	–37	–33	10
5	–16	–14	9
6	3	2	10
7	24	23	9
8	43	39	10
9	61	56	9
10	81	73	9
11	99 (*S*)	91 (*S*,*R*)	10
">90% conversion"			
12	–100 (*R*)	–90 (*R*,*S*)	95
13	–80	–69	>97
14	–61	–49	97
15	–42	–30	96
16	–14	–9	>97
17	4	4	>97
18	27	20	95
19	48	36	>97
20	66	54	94

21	82	72	>97
22	100 (*S*)	91 (*S*,*R*)	97

Determination of the selectivity factor for the palladium-catalyzed allylic substitution reaction



(*R*,*R*)–**3**

In an argon-filled glovebox, an oven-dried vial was charged with $Pd_2(dba)_3 \cdot CHCl_3$ (3.1 mg, 0.0030 mmol), (*R,R*)–**3** (8.3 mg, 0.012 mmol), and naphthalene (internal standard; 21.1 mg, 0.165 mmol). Dichloromethane (anhydrous; 1.08 mL) was added, and the mixture was stirred at rt for 15 min. Next, H_2O (degassed; 120 μL) was added, followed by (±)-cyclohex-2-en-1-yl methyl carbonate (22.3 μL, 23.4 mg, 0.150 mmol). The reaction mixture was stirred at rt. Aliquots (~50 μL) were taken at different reaction times and were immediately quenched by passing through pads of silica, using diethyl ether as the eluent. The conversion and the product ee in each aliquot were determined by chiral GC analysis with a calibrated internal standard: IVADEX-I, N_2, 1.8 mL/min flow-rate, 70–100 °C, 1 °C/min, retention times: 12.2 min ((*S*)-product; major), 12.8 min ((*R*)-product; minor), 22.7 min and 23.0 min (substrate; the peaks for the two enantiomers overlap and were integrated together), 25.5 min (naphthalene). Pure samples of the unreacted starting material were obtained by preparative TLC (silica; pentane:diethyl ether/9:1) of selected aliquots, and their ee was determined by chiral GC analysis: CHIRALDEX-BetaTX, He, 1.0 mL/min flow-rate, 50–180 °C, 5 °C/min, retention times: 16.1 min ((*S*)-substrate; minor), 16.3 min ((*R*)-substrate; major).

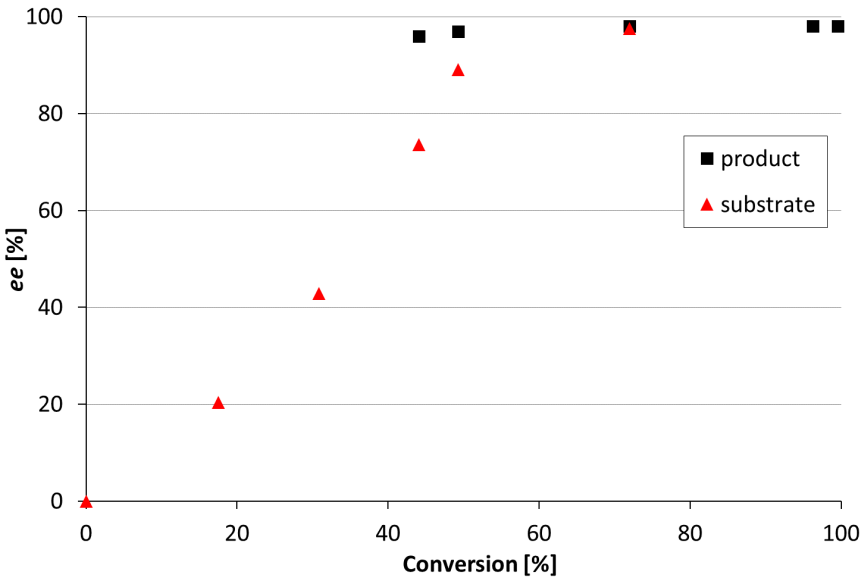


Figure S3. Substrate ee and product ee as a function of conversion in the palladium-catalyzed allylic substitution, starting from racemic substrate ((*R,R*)–**3** was used; the major enantiomer of product is (*S*); the major enantiomer of the unreacted substrate is (*R*)).

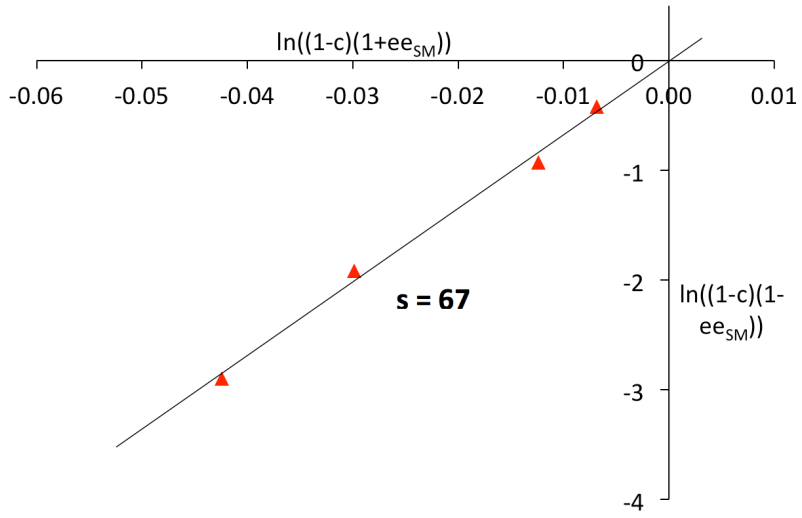
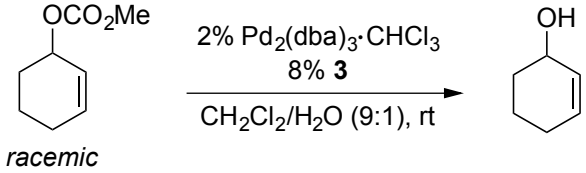


Figure S4. Determination of the selectivity factor (s), based on the data in Figure S3.

Product ee vs. catalyst ee in the palladium-catalyzed allylic substitution reaction (Figure 9)



In an argon-filled glovebox, appropriate amounts (see Table S5, below) of stock solutions of (*S,S*)–**3** (0.025 M in anhydrous dichloromethane) and (*R,R*)–**3** (0.025 M in anhydrous dichloromethane) were mixed in an oven-dried vial (total solution volume: 200 μL). A portion of the resulting solution of ligand **3** (160 μL, 0.004 mmol) was transferred to another oven-dried vial (the remaining solution was used for the determination of the ligand ee; see below). A stock solution of $Pd_2(dba)_3 \cdot CHCl_3$ (0.010 M in anhydrous dichloromethane, 100 μL, 0.0010 mmol) was added to the vial, and the mixture was stirred at rt for 15 min. Next, a stock solution of naphthalene (internal standard; 0.50 M in anhydrous dichloromethane; 100 μL, 0.050 mmol) and H_2O (degassed; 40 μL) were added to the vial, followed by the addition of (±)-cyclohex-2-en-1-yl methyl carbonate (7.4 μL, 7.8 mg, 0.050 mmol). The vial was capped and then removed from the glovebox. The reaction mixture was stirred at rt for 16 h. The reaction was then quenched by passing through a pad of silica, using diethyl ether as the eluent. The conversion (>90% for all of the reactions) and the product ee were determined by calibrated chiral GC analysis: IVADEX-I, N_2, 1.8 mL/min flow-rate, 70–100 °C, 1 °C/min, retention times: 12.2 min ((*S*)-product), 12.8 min ((*R*)-product), 22.7 min and 23.0 min (substrate; the peaks for the two enantiomers overlap and were integrated together), 25.5 min (naphthalene). The ee of the ligand used in the reaction was determined by chiral HPLC analysis of the corresponding phosphine oxide, obtained by oxidation with a solution of *tert*-butyl hydroperoxide (5.0-6.0 M in decane; 5 μL) and purification by preparative TLC (silica; acetone): CHIRALPAK ID column, 40 °C, 2-propanol, 1.0 mL/min flow-rate, retention times: 10.3 min (*S,S*), 13.1 min (*R,R*).

Table S5

Entry	Volume of (*S,S*)–**3** solution (μL)	Volume of (*R,R*)–**3** solution (μL)
1	0	200
2[a]	5	195
3[a]	10	190
4	20	180
5	40	160
6	60	140
7	80	120
8	100	100
9	120	80
10	140	60
11	160	40
12	180	20
13[a]	190	10
14[a]	195	5
15	200	0

[a] Only in the series of reactions run to high conversion.

The second series of reactions was carried out in a similar manner, except that the reactions were quenched after 5 min, instead of 16 h. GC analysis showed that all of the reactions in this series had proceeded to ~10% conversion.

Table S6

Entry	ee_{CAT} (%)	ee_P (%)	conversion (%)
"~10% conversion"			
1	–100 (*S*,*S*)	–97 (*R*)	12
2	–72	–68	11
3	–52	–51	10
4	–34	–32	12
5	–16	–15	11
6	2	3	11
7	23	18	14
8	42	39	11
9	61	56	13
10	78	73	11
11	100 (*R*,*R*)	97 (*S*)	12
">90% conversion"			
12	–100 (*S*,*S*)	–97 (*R*)	>97
13	–95	–51	>97
14	–85	–24	>97
15	–72	–19	>97
16	–52	–9	>97
17	–38	–7	>97
18	–20	–3	>97
19	1	0	>97
20	19	3	>97
21	40	5	>97
22	59	8	>97
23	80	20	>97
24	88	29	>97
25	99	75	>97
26	100 (*R*,*R*)	97 (*S*)	>97